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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,676	02/09/2006	Paul J. Coleman	21481YP	2005

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EXAMINER	
O'DELL, DAVID K	
ART UNIT	PAPER NUMBER
1625	
MAIL DATE	DELIVERY MODE
04/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,676	COLEMAN ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,27-30,34,35 and 37-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,27-30,34,35 and 37-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *24 July 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-17, 27-30, 34-35, 37-40 are pending in the current application.

2. This application is a 371 of PCT/US04/26012 filed 08/11/2004 and claims benefit of the following U. S. Provisional applications: 60/563,580 filed April 19, 2004 and 60/495,637 filed August 15, 2003.

Claim Rejections - 35 USC § 112

1.The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-4, 14, 39, 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds, does not reasonably provide enablement for the protracted list of compounds bearing the protracted list of substituents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of heterocycles, bearing multiple substitutions **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic chemist. **(C) The state of the prior art:** Little prior art exists on these complex compounds, however the synthesis will be evaluated on what is known using scientific principles. **(E) The level of predictability in the art:** Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3.As stated in the preface to a recent treatise:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually

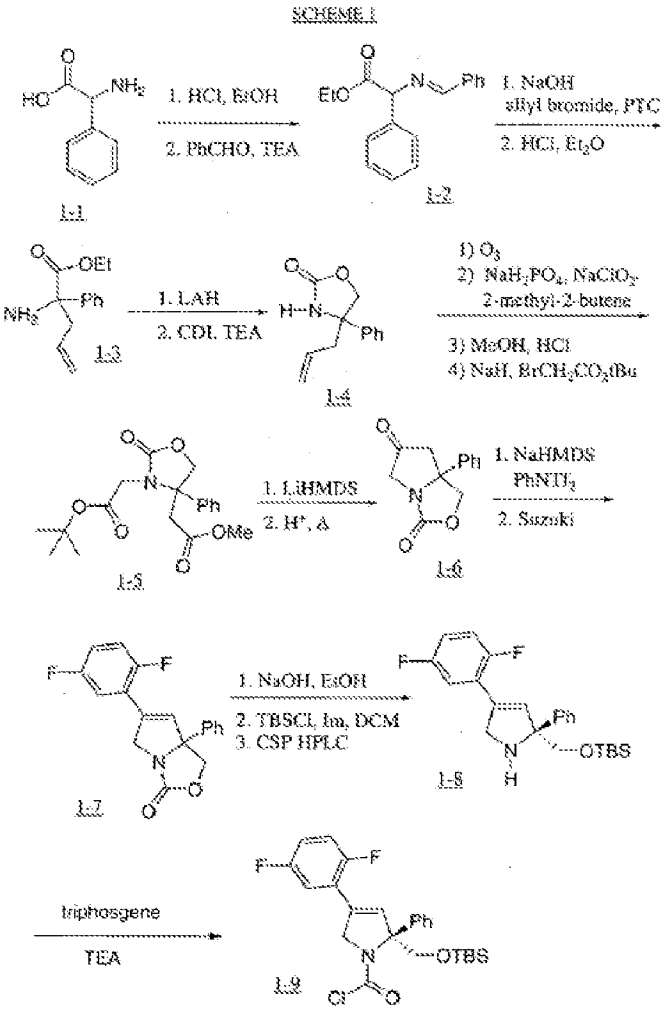
> implies will be able to appraise such work……Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)……..” Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

(F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention: The examiner will first consider the Markush structures I-IV of claims 1-4 respectively, and discuss the limitations inherent to the paucity of available starting materials, as well as the inherent limitations of the chemistry used to prepare the examples; after which the structural requirements for the disclosed utility will be discussed. As per MPEP:

As per MPEP:

> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

Starting from Scheme 1 (reproduced below), which was used to construct the required 2,5-dihydropyrrole 1-9. It is very clear that compound 1-1 gives rise to the substituents R_5, however when looking for α-phenyl glycines (1-1) commercially in the catalog of commercial supplier Sigma-Aldrich (St. Louis, MO)



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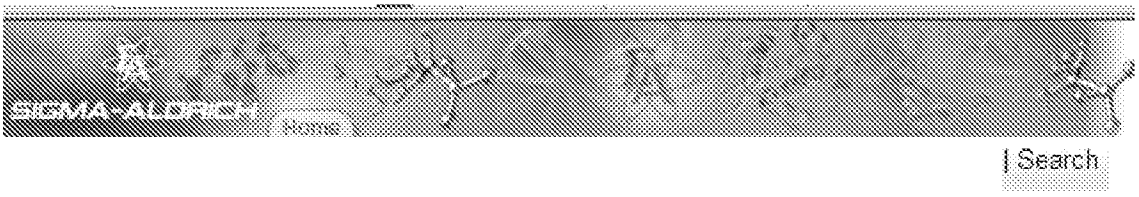
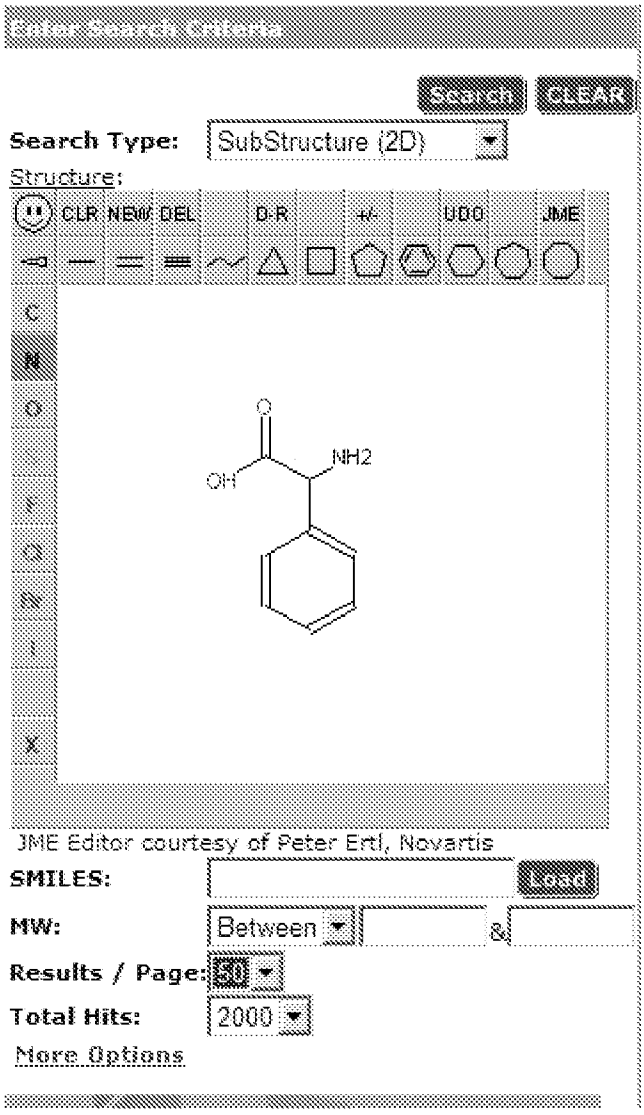
The results of the search of Sigma-Aldrich are shown below:

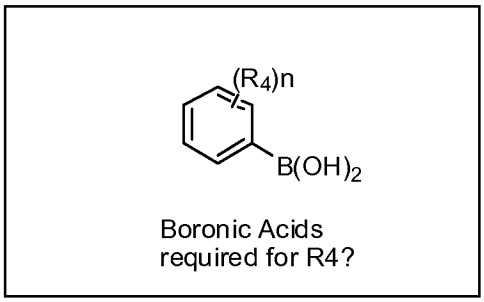




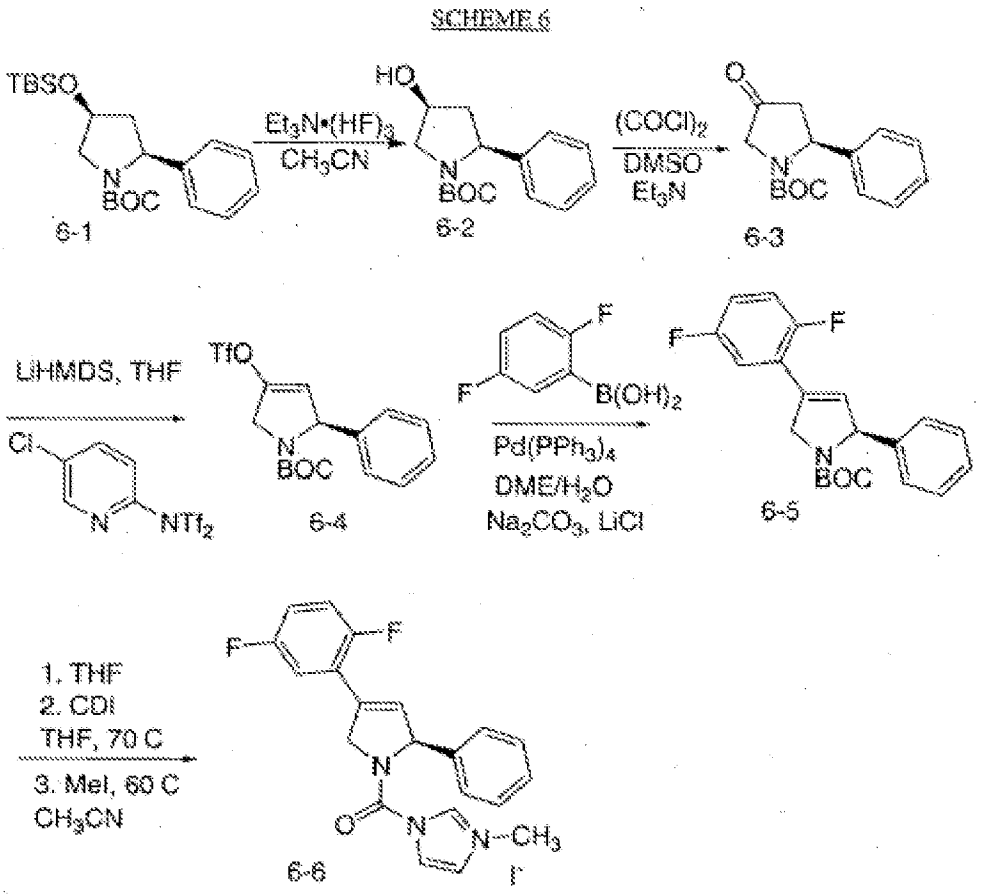
The results are attached as "Commercial 1-1". While 172 compounds appeared, most are redundant i.e. esters or N-alkylated etc. It is very clear that the only compounds available which have the free amino group required to make the imine (1-2), have only F, Cl, and CF3 as

substituents, yet the claims require R5 to be a lengthy list of 12 groups with up to three optional substituents R7 which is itself a list of 20 groups which is then substituted with a list of 9 groups (or in some cases functional groups). What are these materials and how can they be prepared? We have no guidance. Thus the only enabled substituents for R5 are H, F, Cl.

In the conversion of 1-6 to 1-7 we require a vast array of boronic acids (step 2 listed as Suzuki, Scheme 1 or Scheme 6; 6-4 to 6-5)



A search of the catalog of Frontier Scientific (Logan, UT), the largest supplier of a diverse array of boronic acids reveals that only 150 such compounds are commercially available (Attached as "Commercial Boronic Acids"). It is very clear from this list that R4 can only be amino, CF3, acetamide, alkoxy, acetyl, sulfonamide, bromo, chloro, OH, CN, NO_2, fluoro, alkyl, and phenyl at least in terms of starting material availability (more will be said about the chemical limitations in due course). In this case we have 11 possible groups for R4 all which can have up to three optional substituents R7 which is itself a list of 20 groups which is then substituted with a list of 9 groups (or in some cases functional groups). What are these materials and how can they be prepared? We have no guidance.

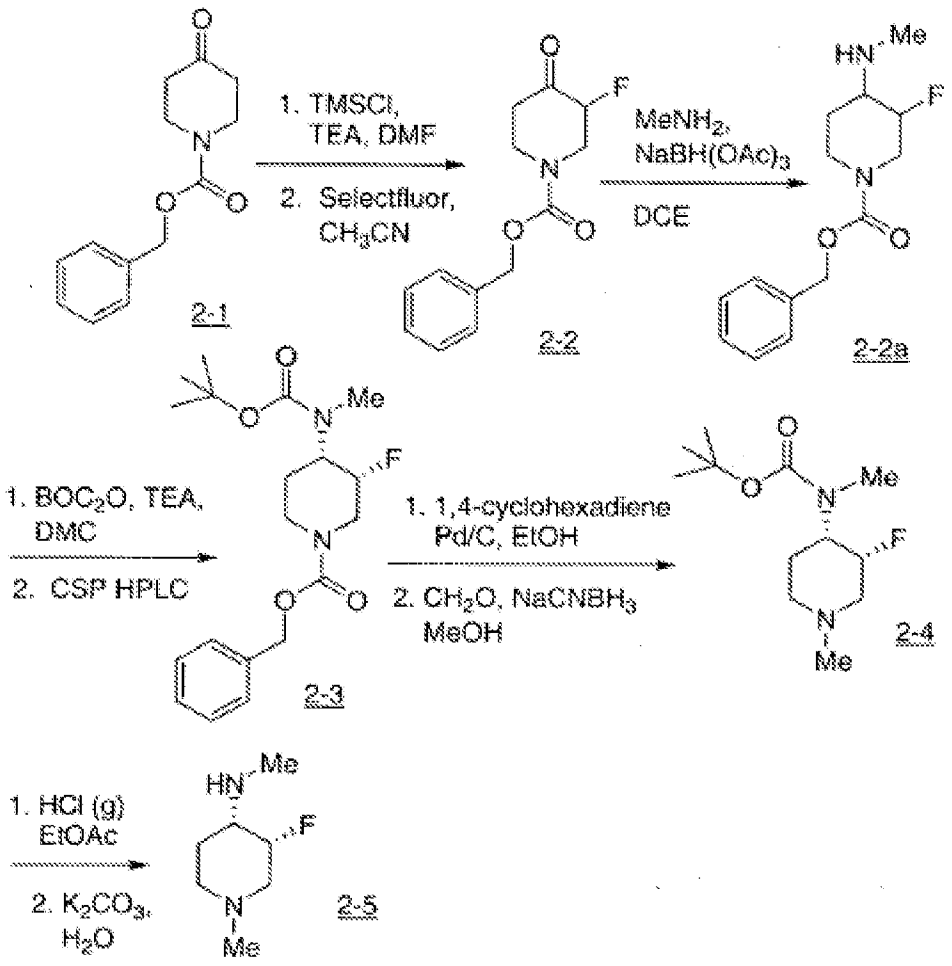


The substituent R_3 arises from the ester of compound 1-3 which is reduced to an alcohol with LAH. The key oxazolidinone 1-4 is then prepared from reaction with carbonyldiimidazole. This core moiety is then carried through until the conversion of 1-7 to 1-8 (Scheme 1). There is at no point a handle to install other substituents, and no chemistry exists for such modifications or has been provided. How can an ester that is reduced with LAH give rise to the lengthy list of 14 substituents groups each optionally substituted with one or more R6 a list 18 substituents? It is very clear that R3 is severely limited by the synthesis and that only CH2OR^d or H is enabled. Remarkably a protracted list of variables for R^d has also been listed pg. 140, claim 1 among

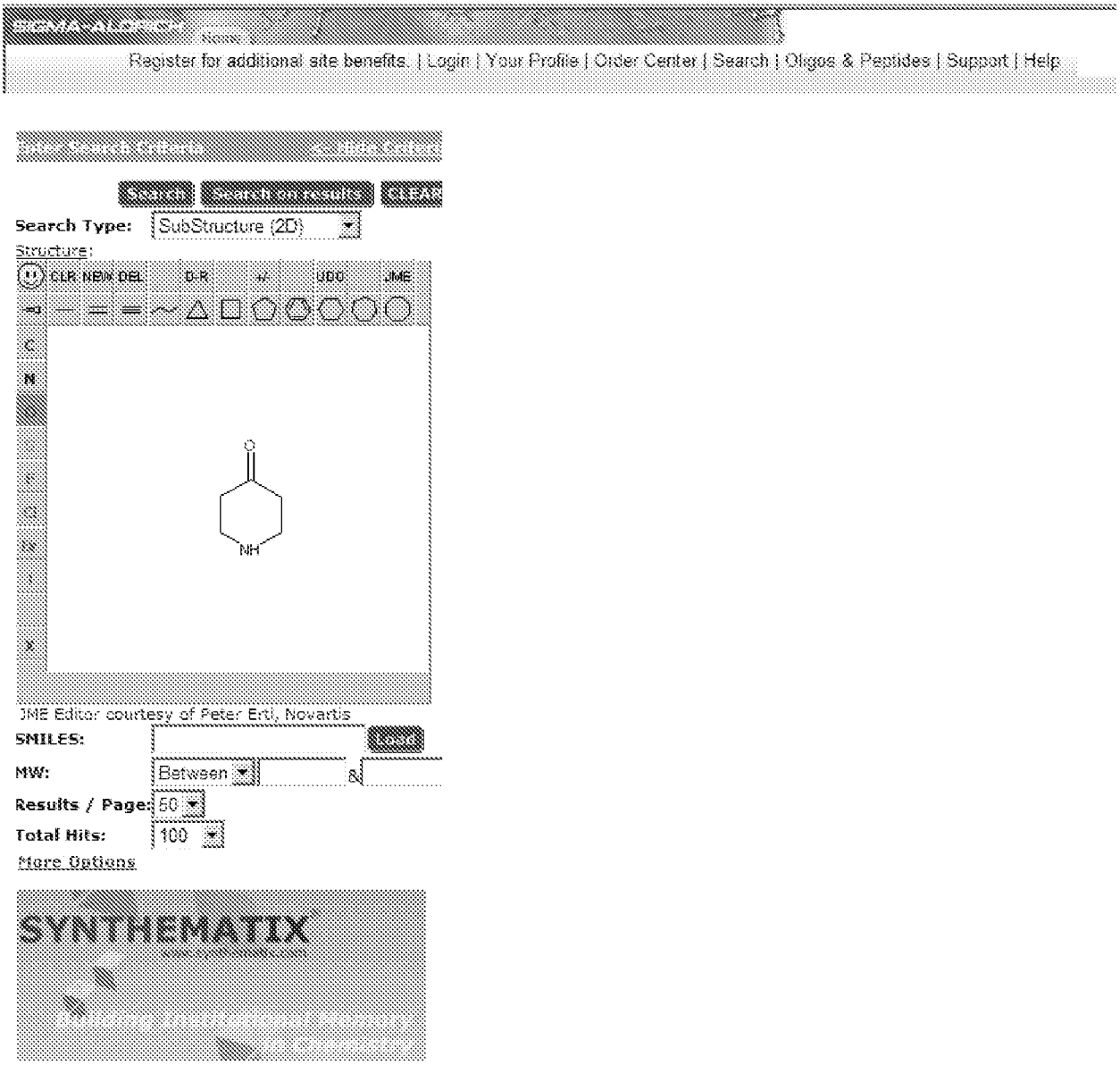
others which is then optionally substituted with up to three R7, which is itself a list of 20 groups which is then substituted with a list of 9 groups (or in some cases functional groups). What are these materials and how can they be prepared? We have been given no guidance. This substituent R3 of claim 1 apparently becomes R2 of claim 13, and a long list of compounds where R2/R3 is other than what is enabled are listed. How can one prepare this long list as on pages 159-162? The strategy given will not result in the compounds claimed. We have the following statement on pg. 110 "The following compounds are prepared by simple modifications of the procedures illustrated in Schemes 1-7 and Schemes G-N, but substituting the appropriately substituted reagents for those utilized in the Schemes." What reagent in which scheme, can give rise to the compounds of claim 13 (i.e. where R2 is the long list of groups?) Only two such syntheses and schemes have been presented namely Scheme 1 and Scheme 6, yet these don't allow for those substituents. How does the oxazolidinone result in other R2(claim 13) or R3 claim 1?

In considering the substituents on the piperidine ring R10-R13 the starting material we are given is the piperin-4-one 2-1 of Scheme 2 reproduced below:

SCHEME 2

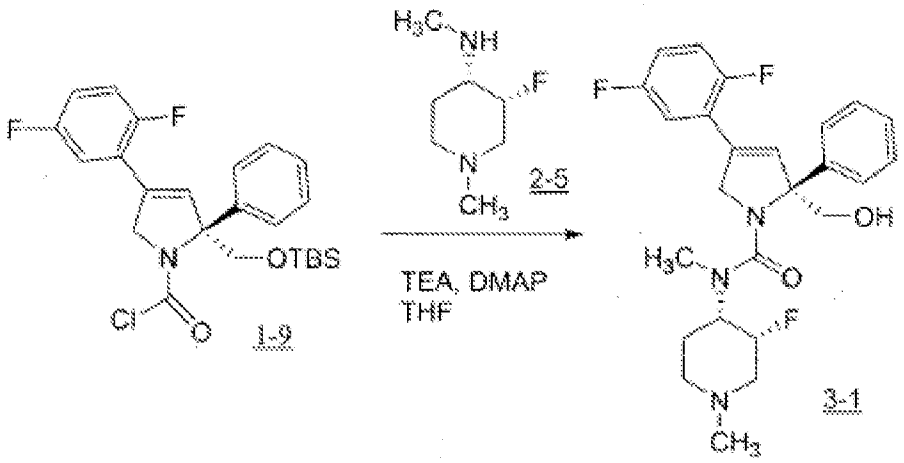


A search for commercially available analogs of 2-1 in the Sigma-Aldrich catalog reveal 129 compounds bearing the core structure (attached as "Commercial 4-piperidinones"), however none have substituents in what is the R_{12} and R_{13} position. The only substituents for R10 and R11 are the conjugated olefins that are dyes (See hits 120-129 for instance.)



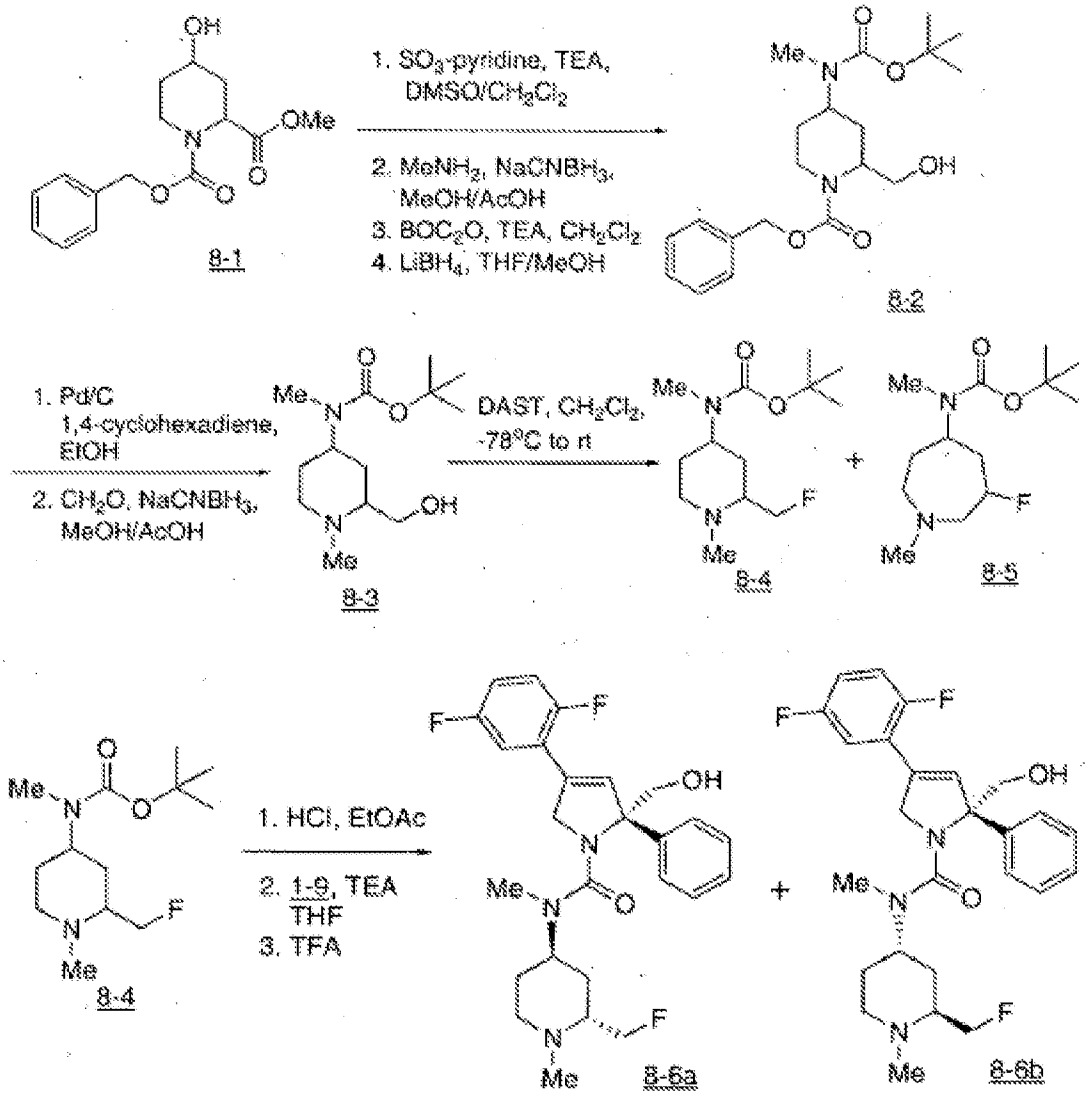
It is very clear that a great deal of effort was expended to install a single F substituent, which must be α to the carbonyl (Scheme 3).

SCHEME 3



Likewise the installation of a single fluoromethylene group for R12 took 7 steps

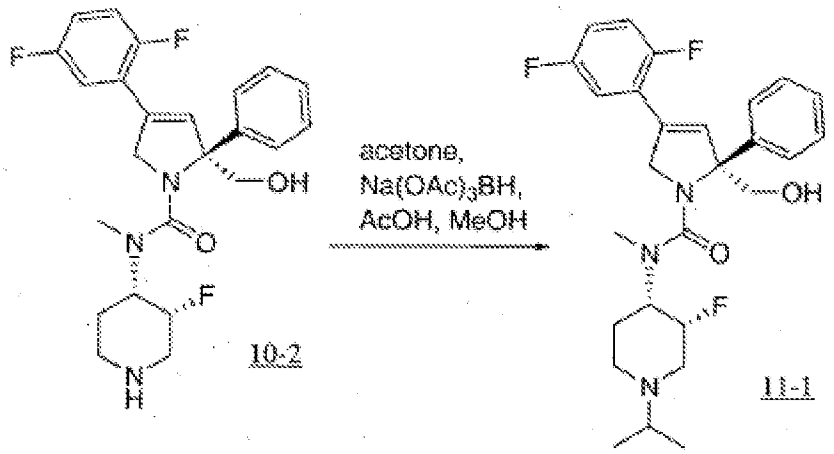
SCHEME 8



Currently no chemistry exists for the preparation of the starting materials required for the scope as claimed. While it is very clear that the starting materials need for the scope are neigher commercial nor can be prepared with known chemistry, it is also clear that even if the cast array of materials were available they would not survive the sometimes brutal and unselective reagents used in the transformations. Several key reagents that are either promiscusous or unselective

will be discussed. The use of Sodium triacetoxyborohydride during reductive amination would reduce the C-X bond (where X is Cl, Br, I) in "optionally halogenated compounds" to the alkanes (Hutchins, R.O. et. al. *J. Org. Chem.* **1977**, *42*, 82-91) (Scheme 11). It is not at all clear to the examiner how these "halogens" could be introduced into the compounds.

SCHEME 11



10-2 11-1

The conversion of 1-7 to 1-8 via the Suzuki-coupling is likewise limited. It is well known in the art that Pd undergoes oxidative addition to "halo" a substituent (readily to I, and Br), which is recited for both R^3 and R^4. The applicant's own disclosure is shown as evidence of this fact. One reviewer has made the following statement about Pd-cataylzed cross-couplings:

> The large number of highly diverse examples of high-yielding Pd-catalyzed organic reactions might give the non-specialist the impression that almost any conceivable transformation might work in the presence of a suitable Pd catalyst. This is, of course, not true, and even the most robust Pd-catalyzed processes have their limitations. Some of these will be discussed in the following sections. The most important unwanted processes which can compete with Pd(0)-catalyzed C-C bond formation include homocoupling or reduction of the halide and homocoupling, C-protonation, or oxidation of the organometallic reagent. (Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim Chapter 8, pgs. 279-308.)

Dorwald has numerous references to reactions that do not work. In particular in the instant case the claims are directed to groups R^4 that will result in undesired processes that do not lead to the product. A variety of cylcometallation process can occur and "give rise to unexpected products or, if the palladacycles are too stable, the catalyst will be consumed and no further reaction will occur." (Dorwald ibid. pgs. 298-299). In addition certain groups can chelate the metal and prevent reaction: "Accordingly, vinyl with strongly chelating ortho-substituents will undergo transition metal-catalyzed C-C bond formation only sluggishly or not at all." (Dorwald ibid. 300-301). It is also a well known limitation of Pd catalyzed reactions that sterically bulky substituents hinder or completely inhibit the reaction.

Remarkably oxonolysis is used to cleave the olefin 1-4 yet somehow olefins on R_5 can survive? The applicants own disclosure is used to show lack of enablement for this substituent. The list of reagents that are incompatable with "optional substituents" could be discussed at length to fill volumes given the scope of the claims. Consider $LiAlH_4$ (Scheme 1), a very promiscuous reductant indeed that will react with nearly any electrophilic functional group ("Lithium Aluminum Hydride" Paquette, L. in *Encyclopedia of Reagents for Organic Synthesis* Online Posting Date: October 15, 2004 2004 John Wiley & Sons, Ltd. "http://www.mrw.interscience.wiley.com/eros/articles/rl036/frame.html"). Triphosgene is even more promiscuous. If the compound 1-8 has a two amines and is treated with phosgene such a diamine will react with at both amines resulting in either diisocyanates or polyisocyanourates and in other instances depending on where the amines are positioned cyclic ureas will be produced. Alcohols and other nucleophiles will under unhibited reactions. This is a good way to make urethanes (see Wagner et. al. U. S. Patent 3,142,699) or mixtures of

polyureas/polyurethanes, or other oligomers (Bachmann et. al. *Macromolecular Chemistry and Physics* **2001**, *202*, 3410-3419; Chen et. al. U.S. Patent 4,477,389).

According to the U.S. Court of Customs and Patent Appeals in *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 101, "[o]rdinarily no problem in this regard arises since the method of preparing almost all starting materials can be set forth in writing if the materials are not already known and available to the workers in the art, and when this is done the specification is enabling to the public". *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, *at the time an application for patent is filed,* (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the situation here. Rather we find very little direction as to how the many required staring materials of formula 1-1, 2-1, and Boronic acids are to be obtained. Where may the directions to prepare or buy them be found?

In re Howarth, 210 USPQ 689, (claimed derivatives of clavulanic acid not enabled by specification lacking information of how prepare the clavulanic acid or directions to reference materials containing such information), *Ex parte Schwarze* 151 USPQ 426 (where starting material is not known to art as of date of filing application, there must be included a description of preparation thereof to enable one skilled in this art to carry out applicant's invention), *Ex parte Moersch* 104 USPQ 122 (claims to process for the production of (1)-y1-p-nitrophenyl-2-dichloracetamindo-propane-1,3-diol not enabled because of failure to describe source or method

of obtaining starting compound; although starting compound is identified by means of appropriate name and by structural formula).

It does seem highly probable that variability on R_2 (of Formula 1) can be achieved with reductive amination however we know that the limitations of the synthesis are but one limitation of these geni and sub-geni. Some of the most important limitations are those required for activity at the KSP target. Indeed the compounds of the instant case were modeled on the 3,5-diaryl-4,5-dihydropyrazoles as evidenced by the statement regarding these compounds:

> "We recently reported the development of 3,5-diaryl-4,5-dihydropyrazoles as potent and cell-active KSP inhibitors. [7] These compounds demonstrated high selectivity for KSP versus other kinesins, a consequence of their allosteric mode of binding. Part of our efforts to expand the scope of this series centered on modifications to the core structure designed to improve reactivity in amide bondforming reactions and to preserve the orientation of the two aryl groups to maintain potency. **We rationalized that a 2,5-dihydropyrrole nucleus might serve as a viable replacement for the 4,5-dihydropyrazole core in that the hybridization of the aryl-bearing carbon atoms would be maintained, allowing for a similar presentation of the diaryl array** (Fig. 1)."

Mark E. Fraley, Robert M. Garbaccio, Kenneth L. Arrington, William F. Hoffman, Edward S. Tasber, Paul J. Coleman, Carolyn A. Buser, Eileen S. Walsh, Kelly Hamilton, Christine Fernandes, Michael D. Schaber, Robert B. Lobell, Weikang Tao, Victoria J. South, Youwei Yan, Lawrence C. Kuo, Thomayant Prueksaritanont, Cathy Shu, Maricel Torrent, David C. Heimbrook, Nancy E. Kohl, Hans E. Huber and George D. Hartman "Kinesin spindle protein (KSP) inhibitors. Part 2: The design, synthesis, and characterization of 2,4-diaryl-2,5-dihydropyrrole inhibitors of the mitotic kinesin KSP" *Bioorganic & Medicinal Chemistry Letters* **2006**, *16*, 1775–1779. In the work on the 3,5-diaryl-4,5-dihydropyrazoles (Christopher D. Cox, Michael J. Breslin, Brenda J. Mariano, Paul J. Coleman, Carolyn A. Buser, Eileen S. Walsh,

Kelly Hamilton, Hans E. Huber, Nancy E. Kohl, Maricel Torrent, Youwei Yan, Laurence C. Kuo and George D. Hartman "Kinesin spindle protein (KSP) inhibitors. Part 1: The discovery of 3,5-diaryl-4,5-dihydropyrazoles as potent and selective inhibitors of the mitotic kinesin KSP" *Bioorganic & Medicinal Chemistry Letters* **2005**, *15*, 2041–2045) the substitution pattern on the two phenyl rings was deemed critical it was stated: "the lack of potency in the unsubstituted analog **3** indicated that substitution on each ring was critical for activity." Moreover Fraley et. al. stated that in compound **13** (a compound of the instant case) far more subtle interactions governed the ability of these materials to interact with the target: "Adoption of this rotamer conformation directs the methyl group of **13** into a hydrophobic region just below the plane of the dihydropyrrole core, further increasing the binding energy" (ibid. 1777 col. 2 discussion). Indeed it is clear that the position of the rotamer governs activity, and no one would argue that the identity and positions of substitutions in the compounds of the instant would have a predictable effect on the nature of the conformation of the rotamer. The only information provided to the examiner in so far as activity of the compounds is concerned is a single statement "The compounds 3-1, 4-2, 5-3, 5-4, 7-1, 7-2, 7-3, 8-6a/8-6b, 9-1, 10-2, 11-1, 12-1, 12-2 and 12-3 in the Examples were tested in the above assay and found to have an IC50 50uM.". At least from the information given the other species apparently were inactive or less active.

The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification , at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510,

1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has few working examples in this unpredictable art without undue experimentation.

4. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention
In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

When one of these factors is being referred to specifically, a bold letter will appear after a statement or discussion to indicate the particular Wands factor being referred to. This is pharmaceutical invention requiring the treatment of all cancers, which are different diseases such as colon cancer, pancreatic cancer, breast cancer, brain cancer, lung acner etc. with compounds. **(B)** One of ordinary skill is a medical doctor or Pharm D. **(D)** In the instant case we have been given very little information as to what these compounds are doing in the pharmacological sense. It is very clear from the data given in the specification that the compounds was tested in an in-vitro enzyme inhibition assay. **(F)**. The claims are extremely broad encompassing a large

number compounds (claim 1) and compounds that are by applicants own data inactive. **(A)**. The inventor has provided no working examples of the treatment of any diseases. **(G)** In terms of the correlation between the assays given here and the diseases under the claims (colon cancer, breast cancer, restenosis), there is no correlation between the assays given and the disease state.

As per MPEP 2164.02:

CORRELATION: IN VITRO /IN VIVO
The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications). Since the initial burden is on the examiner to give reasons for the lack of enablement**, the examiner must also give reasons for a conclusion of lack of correlation for an in vitro or in vivo animal model example.** A rigorous or an invariable exact correlation is not required, as stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985): [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

The existence of such a "silver bullet" is contrary to our present understanding of oncology. Simone, Oncology: Introduction, *Cecil Textbook of Medicine*, 20th Edition, 1996 Vol. 1, pp. 1004-1010, states that, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study' (see the enclosed article, page 1004). A 'disease caused by proliferation of tumor cell' is anything that is caused by abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued

growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see In re Buting, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers. The ideal chemotherapeutic drug would target and destroy only cancer cells without adverse effects or toxicities on normal cells. Unfortunately, no such drug exists; there is a narrow therapeutic index between cell kill of cancer cells and that of normal cells. Successful treatment of cancer requires elimination of all cancer cells, whether at the primary site, extended to local-regional areas, or metastatic to other regions of the body. The major modalities of therapy are surgery and radiotherapy (for local and local-regional disease) and chemotherapy (for systemic sites). For example, regarding the treatment of leukemia, The Merck Manual (online edition) states, that "Treatment programs and clinical situations are complex". Dosage regimen is dependent on several risk factors and the contribution of each active ingredient of a multidrug combination therapy is complex and unclear. Similarly, Myelodysplastic syndrome (MDS) is characterized by clonal proliferation of hematopoietic cells, including erythroid, myeloid, and megakaryocytic forms and its incidence is unknown and further, there is no established treatment. Several growth factors and their receptors have been associated with glioma and the treatment depends on the pathology and location and is often multimodal. Cell line data for cancer drugs is well-known to be unpredictive of treatment, even animal data is not predictive see Trisha Gura "CANCER

MODELS: Systems for Identifying New Drugs Are Often Faulty" Science 7 November 1997: Vol. 278. no. 5340, pp. 1041 - 1042:

"Indeed, since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the U.S. Food and Drug Administration. "**The fundamental problem in drug discovery for cancer is that the model systems are not predictive at all**," says Alan Oliff, executive director for cancer research at Merck Research Laboratories in West Point, Pennsylvania."

The correlation between in vitro cancer models and clinical expetations has been summarized:

> "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation in vitro, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and, thereby, drug access to the tumor cells are not evenly distributed and this fact consists an important source of heterogeneity in tumor resonse to drugs that does not exist in vitro. **Therefore, prediction of drug effects in cancer patients based solely on in vitro data is not reliable and further evaluation in animal tumor systems is essential.**" Zips et. al. "New Anticancer Agents: In Vitro and In Vivo Evaluation" *in vivo* 2005, 19, 1-8. **(E)**

For in vivo models, a retrospective National Cancer Institute Study examined 39 drugs using transplantable human tumor cell lines and compared them to phase II clinical outcomes. (See Johnson, et. al. "Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials." *British Journal of Cancer* **2001**, *84*, 1424–1431.) The *in vivo* xenograft data was not predictive of activity against the same human tumors. In the instant case there is not even cell based data to rely upon. There is no clear nexus between enzyme inhibiton (KSP) and the cancer treatment claimed here.

The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would

not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation.

6. Claim 28-30, 34-35, 37-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to methods of treatment with the compounds of the instant claims and other unknown materials defined by function some of which are described by a negative function "inhibitor of a mitotic kinesin that is not KSP". The Wands factors are listed above in previous rejection. A few are summarized here: **(F) The amount of direction provided by the inventor:** No evidence of synergism between the compounds of the instant case and a "serine threonine kinase inhibitor" or an "inhibitor of a mitotic kinesin that is not KSP" is presented. **(C) The state of the prior art: (E) The level of predictability in the art:** The prior art teaches that cancer treatment is difficult (*supra*) ond not shown with these compounds. Moreover the claims require at least one other active compound of unaccertainable scope, however Borisy et. al. "Systematic discovery of multicomponent therapeutics" PNAS **2003**, *100*, 7977–7982.

> "In some instances, a synergistic combination that we, to our knowledge, discovered empirically will have relevant citations in the literature such that it may appear to have been almost predictable with hindsight. **However, many other equivalent predictions would also be made from the literature and these usually do not result in synergy when tested experimentally. In this sense, biological literature contains many anticipatory observations and**

> **speculations regarding connections between pathways (and compounds), most of which do not ultimately prove to be synergistic when tested directly**."

(G) The existence of working examples: No working examples exist**; (H) The quantity of experimentation needed to make or use the invention:** The correlation between the hypothetical synergism of a compound that does not necessarily function as a cancer treatment, with perhaps billions of other compounds ("a cytotoxic/cytostatic agent" "inhibitor of a mitotic kinesin that is not KSP" etc.) is not shown. The amount of experimentation required approaches the infinite. See Grant R. Zimmermann "Multi-target therapeutics: when the whole is greater than the sum of the parts." *Drug Discovery Today* **2007**, *12*, 34-42.

> "The success of the combination drugs discussed justifies efforts to identify novel multi-target therapeutics early in the discovery process, **but the systematic pursuit of combination drugs presents unique experimental challenges. First, multi-target therapies rely upon complexity in the disease system, which must be reproduced in vitro for discovery screening. Second, without a priori knowledge of target pairs that interact synergistically, the vast space of possible target combinations needs to be covered by an agnostic search. Finally, the sensitivity of synergistic interactions to dosing ratios requires substantial experimental investment and specialized analyses for each combination tested**.....because the number of combinations expands quadratically with the number of agents being tested, multi-target discovery efforts are usually constrained by the efficiency of the screening platform available. For example, **even a small set of 2000 agents generates almost two million unique pairwise combinations**."

It is very clear that undue experimentation is required. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification , at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 7,235,580. Although the conflicting claims are not identical, they are not patentably distinct from each other because they cover the same compounds. For example a species of the claim 8 (580):

4-(2,5-Difluorophenyl)-2-(hydroxymethyl)-N-methyl-N-(1-methylpiperidin-4-yl)-2-phenyl-2,5-dihydro-1H-pyrrole-1-carboxamide;

and numerous others of the hundreds of compound therein.

6. Claims 1-17, 27-30, 34-35, 37-40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16, 20 of copending Application No. 10/517,559. Although the conflicting claims are not identical, they are not patentably distinct from each other because they have individual compounds that overlap as well as the generic claims for example a species of claim 15,:

20 4-{[4-(2,5-difluorophenyl)-2-phenyl-2,5-dihydro-1H-pyrrol-1-yl]carbonyl}piperidin-4-amine;

anticipates the generic and is claimed in the instant case. Also compound 35-16, and numerous others of the hundreds of compound therein.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Statutory Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

7. Claims 1-17, 27-30, 34-35, 37-40 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-14 & 18 of copending Application No. 10/915,743. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Double patenting warning

8. It is noted that the applicant has numerous copending applications with the same title:

10/520,492
10/506,702
10/515,285
10/559,855
10/567,314
10/568,000
10/537,217
10/916,096
11/040,522
11/630,224
11/793,090
10/567,249
11/630,303

The burden is now shifted to the applicant to point out anymore instances of double patenting.

Claim Rejections - 35 USC § 102

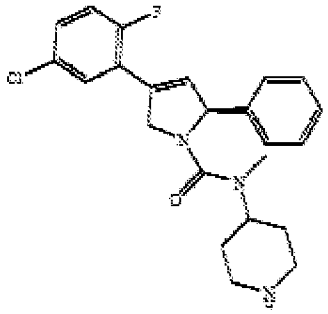
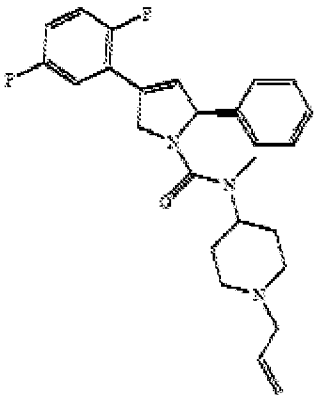
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1, 2 & 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Arrington, et. al. US Pre-Grant Publication 2006/0105997. The applied reference has a common assignee and some inventors with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed

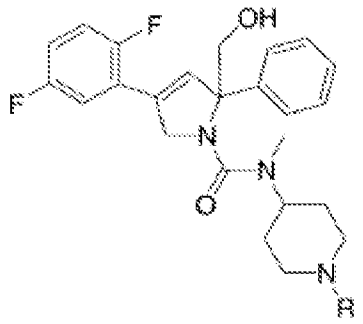
but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

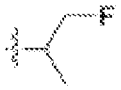
Support can be found in U.S. Provisional 60/403,830 filed 8/15/02 which antedates the filing date of the instant case. A few species are shown here, others are present:

Cmpd	Structure	Name	LRMS m/z (M + H)
18-5		(2S)-4-(5-chloro-2-fluorophenyl)-N-methyl-1-phenyl-N-(piperidin-4-yl)-2,5-dihydro-1H-pyrrole-1-carboxamide; isolated as the TFA salt	LRMS m/z (M + H) 414.0 found, 414.1 required.
18-13		(2S)-N-(1-allylpiperidin-4-yl)-4-(2,5-difluorophenyl)-N-methyl-2-phenyl-2,5-dihydro-1H-pyrrole-1-carboxamide; isolated as the TFA salt	LRMS m/z (M + H) 438.1 found, 438.2 required.

10. Claims 1, 2 & 14 rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Pre-Grant Pub 2006/01000191 also U.S. Patent 7,235,580

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. Support is found in U.S. Provisional 60/419,570 filed October 18, 2002. Some species are shown here:



Compound No.	R	HRMS (calculated)	HRMS (found)
17-3		470.2614	470.2614
17-4		456.2457	456.2449
17-5		482.2614	482.2603
17-6		488.2520	488.2517
17-7		506.2425	506.2408

Specification Objections

11. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "2,4-diaryl-2,5-dihydropyrrole Inhibitors of the Mitotic kinesin KSP"

Conclusion

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Rita Desai can be reached on (571) 272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625